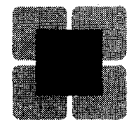

Outcome of primary cytoreduction surgery for advanced epithelial ovarian carcinoma

DAVID B. SEIFER, MD*; ALEXANDER W. KENNEDY, MD; KENNETH D. WEBSTER, MD; SHARON VANDERBRUG MEDENDORP, MPH; DINAH G. ISAKSON, BA, ART

■ Seventy-nine consecutive patients with Stage III or IV epithelial ovarian carcinoma underwent primary cytoreduction surgery at the Cleveland Clinic over a 10-year period (1975 to 1985). Optimal cytoreduction, defined as a residual with a diameter of 2 cm or less, was achieved in 35 patients (44.3%). Women with disease that could undergo cytoreduction with optimal results had greater chances of survival without significantly increased risk for postoperative morbidity or mortality than those in whom results were not optimal. Multivariate stepwise logistic regression analysis revealed four covariates (stage of disease, cell type, distended abdomen, and age at operation) that were independently significant in predicting the ability to reach an optimal state at the completion of cytoreductive surgery. Multivariate stepwise Cox proportional hazards regression analysis revealed cytoreductive status, stage of disease, ascites, eligibility for second-look laparotomy, and parity to be factors significantly related to survival. Until prospective studies are completed, cytoreductive surgery remains the state of the art for the treatment of advanced epithelial ovarian carcinoma.

□ INDEX TERM: OVARIAN NEOPLASMS, SURGERY □ CLEVE CLIN J MED 1988; 55:555–560

CARCINOMA of the ovary is the leading cause of mortality from gynecologic malignancies in the United States, with an estimated 14,000 deaths in 1986. At that time, it ranked third in incidence with 19,000 cases, after endometrial and cervical carcinomas.[1] The high mortality is attributable in part to the difficulty of early detection; 70% of women with ovarian carcinoma have advanced disease at the time of initial diagnosis.

A multi-modality approach is standard for women with advanced epithelial ovarian cancer. Aggressive cytoreductive surgery (debulking) at the time of initial laparotomy, combination chemotherapy, and later surgical re-exploration in patients clinically free of disease is the treatment plan that has been adopted by most gynecologic oncologists. The efficacy of these therapies will require evaluation as randomized, prospective studies are completed. In the interim, cytoreductive surgery has become the cornerstone for optimizing conditions for chemotherapy with curative intent in patients with advanced disease.

■ *See also the editorial by Macfee (pp 511–512)*

The purpose of this study is to review the experience at the Cleveland Clinic involving cytoreductive surgery

From the Departments of Gynecology and Biostatistics and Epidemiology, The Cleveland Clinic Foundation. Submitted Aug 1987; accepted Jan 1988.

Address reprint requests to A.W.K., Department of Gynecology, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

*Present address: Department of Obstetrics and Gynecology, SUNY Health Center, Syracuse, New York 13210.

TABLE 1
PARAMETERS CONSIDERED FOR PROGNOSTIC SIGNIFICANCE FOR OPTIMAL DEBULKING STATUS

Age
Menopause status
Race
Gravidity
Parity
Gastrointestinal symptoms
Distended abdomen at presentation
Stage
Grade
Cell type
Pelvis (maximum metastatic tumor diameter)
Abdomen (maximum metastatic tumor diameter)
Ascites
Bowel surgery

for advanced epithelial ovarian carcinoma. This study was designed to determine the feasibility and morbidity of cytoreductive surgery, the efficacy of cytoreductive surgery as measured by survival, and the factors associated with achieving an "optimal" state for the patient at the completion of cytoreductive surgery.

MATERIALS AND METHODS

From January 1975 to December 1985, 79 consecutive patients with previously untreated Stage III and IV epithelial ovarian carcinoma underwent primary cytoreductive surgery at the Cleveland Clinic. Pertinent clinical records were reviewed. Primary cytoreductive surgery was defined as the first surgical effort to reduce a patient's tumor mass to a diameter of 2 cm or less. Of those 79 patients with advanced epithelial ovarian cancer, 54 (68.4%) were FIGO Stage III and 25 (31.6%) were FIGO Stage IV.

Seventy-two (91.1%) of the patients were white, six (7.6%) were black, and one (1.3%) was Hispanic. The median age at time of surgery was 58.1 years (range, 33.9–80.2 years). Eighteen patients (22.8%) were younger than 50. Forty-six patients (58.2%) were between the ages of 50 and 70, and 15 patients (19.0%) were older than 70. There were 63 serous, 3 mucinous, 3 endometrioid, 7 clear-cell, and 3 unclassified carcinomas. Eight were well differentiated, 23 moderately differentiated, 41 poorly differentiated, and 7 undifferentiated.

Seventy-seven patients were referred directly to the Cleveland Clinic for primary cytoreductive surgery, whereas two had undergone laparotomy and biopsy in order to establish a diagnosis and received two cycles or fewer of chemotherapy before referral and re-exploration for primary cytoreductive surgery. One patient had received a single course of platinum-based chemotherapy prior to cytoreductive surgery and the other had received two courses of doxorubicin-cyclophosphamide therapy prior to definitive surgery. Thirty (88.2%) patients in the optimal group received combination chemotherapy, including cis-platin, after cytoreductive surgery. Thirty-one (68.8%) patients in the suboptimal group received a cis-platin-containing combination chemotherapy regimen. Those not receiving cis-platin because of compromised renal function received other chemotherapeutic agents. Three patients died before chemotherapy could be started.

TABLE 2
SITES OF DISEASE INVOLVEMENT

Sites	Number of patients
Right ovary	72
Right fallopian tube	42
Left ovary	73
Left fallopian tube	44
Uterus	41
Pelvic peritoneum	37
Bladder peritoneum	34
Sigmoid	27
Cul-de-sac	32
Pelvic lymph node	9
Paraaortic lymph nodes	21
Infracolic omentum	62
Supracolic omentum	21
Large bowel	31
Small bowel	38
Paracolic gutters	36
Diaphragm	54
Liver parenchyma	19
Liver capsule	26
Renal capsule	7
Appendix	8
Stomach	6
Spleen	1
Gallbladder	1
Pancreas	1
Anterior abdominal peritoneum	19
Extrabdominal metastases (lung)	6

The associations of factors of suspected prognostic significance with debulking were evaluated with the chi-square test, Fisher's exact test, and Student's *t*-test (*Table 1*). To identify characteristics of a patient most likely to have optimal cytoreduction, we further examined the factors indicating prognostic significance within the framework of multivariate stepwise logistic regression.[2] Patient survival was estimated using the Kaplan-Meier method. The significance of the differences in survival distributions for various subgroupings of factors was tested with the log rank test. Factors that indicated prognostic significance were then investigated in

TABLE 3
OPERATIONS PERFORMED DURING CYTOREDUCTIVE SURGERY

Procedure	Number of patients
Total abdominal hysterectomy*	44
Subtotal abdominal hysterectomy	10
Bilateral/unilateral salpingo-oophorectomy†	73
Omentectomy	65
Large bowel resection with colorectal anastomosis	7
Large bowel resection with Hartman pouch	7
Small bowel resection with reanatomosis	5
Diverting colostomy	3

* Previous hysterectomy for benign pathology: 8
† Previous unilateral salpingo-oophorectomy: 6

the multivariate context of a Cox proportional hazards regression model.[3] Statistical significance was tested at the $P=0.05$ level for all tests.

RESULTS

Cytoreduction was optimal in 35 patients (44.3%) with Stage III and IV epithelial ovarian carcinoma but was suboptimal in 44 (55.7%). Inability to achieve suboptimal cytoreduction was associated with disease of the diaphragm, paracolic gutters, or small bowel. Cytoreduction was optimal in 30 patients (55.5%) with Stage III disease but in only 5 (20%) with Stage IV disease.

At the time of laparotomy, the most common sites of tumor involvement were the right and left ovaries, infracolic omentum, and undersurfaces of the diaphragm. Sites of the largest tumors were the ovaries and infracolic and supracolic omentum.

The largest metastatic tumors ranged between 0.5 and 28.0 cm in diameter (mean, 9.4 cm; median, 10.0 cm). In 47 patients (58.5%), the largest metastasis was confined to the pelvis; in another 32 (41.5%), the largest metastasis was in the abdomen. *Table 2* lists the disease sites and the number of patients with disease at those sites.

Operations performed during primary cytoreductive surgery were, in order of decreasing frequency: bilateral/unilateral salpingo-oophorectomy, omentectomy, total abdominal hysterectomy, large-bowel resection, subtotal abdominal hysterectomy, small-bowel resection, and (diverting) colostomy (*Table 3*).

The mean blood loss was 1,012 mL (range, 200–3,000 mL) for patients in the optimal group compared with 1,170 mL (range, 100–4,000 mL) for patients in the suboptimal group. The mean number of transfused units of packed red blood cells was 2.6 (range, 0–7) for the optimal group and 3.0 (range, 0–9) for the suboptimal group.

Ascites was found in 61 patients (77.2%). The median amount of ascitic fluid noted at laparotomy was 1,850 mL (range, 100–8,000 mL) in the optimal group compared with 3,250 mL (range, 100–9,500 mL) in the suboptimal group. The median operative time was three hours (range, 1.5–5 hours) for the optimal group and 2.9 hours (range, 1.5–6 hours) for the suboptimal group.

The median postoperative hospital stay was 12 days (range, 7–24 days) for the optimal group and 13 days (range, 7–56 days) for the suboptimal group.

Postoperative morbidity occurred in 32 patients (40.5%). The most common causes of minor morbidity in both groups were fever (12 [15.2%]) and ileus (10 [12.6%]). Congestive heart failure, pulmonary embolism, and wound infection developed in one patient in each group. In the optimal group, two patients suffered from a cerebrovascular accident and one patient contracted pneumonia. In addition, the suboptimal group included one patient with wound dehiscence, two with deep venous thrombosis, and one with an enterocu-

TABLE 4
MORBIDITY AND MORTALITY IN OPTIMAL AND SUBOPTIMAL GROUPS ASSOCIATED WITH CYTOREDUCTIVE SURGERY

	Optimal	Suboptimal
Minor Morbidity		
Fever	5	7
Ileus	4	6
Urinary tract infection	1	1
TOTAL	10	14
Major Morbidity		
Pneumonia	1	0
Congestive heart failure	1	1
Wound infection	1	1
Dehiscence	0	1
Deep venous thrombosis	0	2
Pulmonary embolism	1	1
Cerebral vascular accident	2	0
Fistula	0	1
Mortality	1	2
TOTAL	7	9

TABLE 5
BOWEL SURGERY PERFORMED DURING CYTOREDUCTIVE SURGERY

Type of Surgery	Optimal	Suboptimal	TOTAL
Sigmoid resection with reanastomosis	3	4	7
Sigmoid resection with Hartman pouch	2	5	7
Small bowel resection with reanastomosis	3	2	5
Diverting colostomy	1	2	3
TOTAL	9	13	22

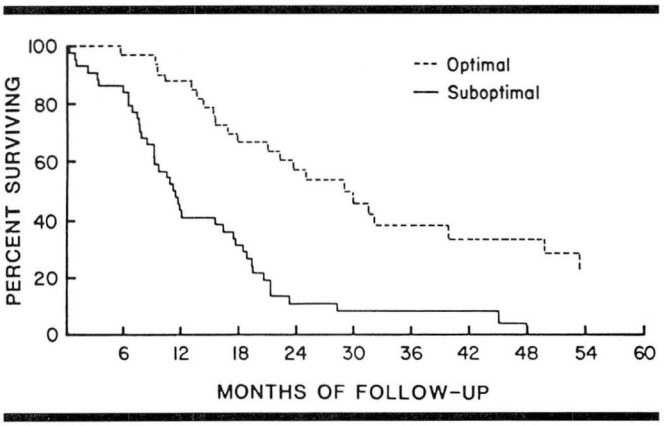

FIGURE 1. Survival of patients with optimal *v* suboptimal cytoreduction.

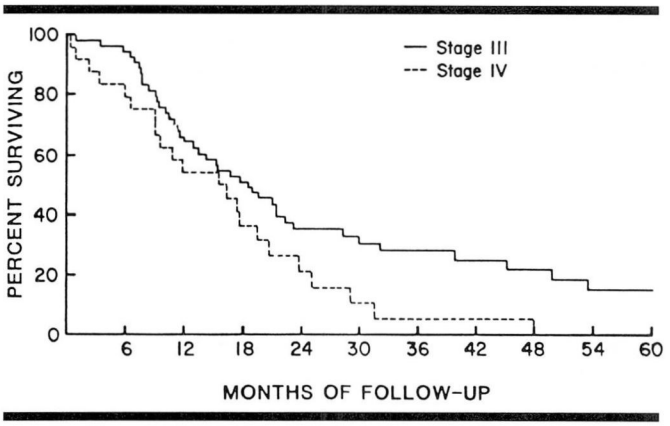

FIGURE 2. Survival of patients with Stage III *v* Stage IV disease.

taneous fistula. There was no significant statistical difference in morbidity or mortality between optimal and suboptimal groups (*Table 4*).

Bowel surgery was performed in nine patients (25.7%) in the optimal group and 13 (29.5%) in the suboptimal group (*Table 5*). There was no significant statistical increase in postoperative morbidity in patients undergoing bowel surgery as part of cytoreductive surgery.

Three patients (3.7%) died postoperatively. In two cases, preoperative pulmonary emboli from deep venous thrombosis had developed, and in the third case, the inferior vena cava was clipped at the time of cytoreduction. Following surgery, one patient experienced cardiopulmonary arrest secondary to a presumed pulmonary embolism, and another died of acute renal failure. The third patient died due to septicemia. Two of these three patients were in the suboptimal group.

Twenty patients (57.1%) in the optimal group were clinically free of disease after chemotherapy and underwent second-look laparotomy to detect persistent occult disease. Seven of these 20 (35.0%) showed no evidence of disease and discontinued chemotherapy. Presently, five of these seven patients are alive without evidence of disease.

Five patients (11.4%) in the suboptimal group showed no clinical evidence of disease after chemotherapy. Four underwent second-look laparotomy, and all were found to have persistent disease. No detectable disease was evident in one patient who underwent second-look laparoscopy because of her poor medical status.

The factors significantly associated with suboptimal debulking status were stage of disease (P=0.003), metastatic tumor of diameter greater than 10 cm in the abdomen (P=0.007), distended abdomen (P=0.024), serous cell type (P=0.027), and age at time of surgery (P=0.068). These factors were then included in the risk set for stepwise multivariate logistic regression to determine their ability to predict optimal status after cytoreductive surgery. This analysis indicated stage of disease, cell type, distended abdomen, and age at operation to be prognostically significant. Notably, tumor grade, bowel surgery, ascites, and parity were not independent variables significantly related to debulking status.

In the optimal group, 25 patients (71.4%) died of ovarian cancer, one (2.9%) was alive with cancer, and nine (25.7%) were alive without clinical evidence of cancer from 20 months to eight years after surgery. Three patients (6.7%) in the suboptimal group were alive with disease from 16 to 37 months after surgery.

The relationships of various prognostic factors to survival were examined univariately using Kaplan-Meier curves and the log rank test and then multivariately with the stepwise Cox proportional hazards regression model. Debulking status (P=0.001), eligibility for second-look laparotomy (P=0.037), nulliparity (P=0.037), stage of disease (P=0.037), and ascites (P=0.05) were all significantly related to survival. Notably, tumor grade, cell type, age, bowel surgery, and size of primary tumor in the pelvis or abdomen were not significantly related to survival.

Figures 1 through *3* show the Kaplan-Meier curves for subgroups of debulking status, stage, and ascites. The median survival was 29 months for patients who had optimal cytoreduction and 11 months for those with suboptimal cytoreduction (*Figure 1*). The one- and three-year survival rates were 88% and 57% for the optimal group and 41% and 11% for the suboptimal group. For those with Stage III disease, median survival was 18.4

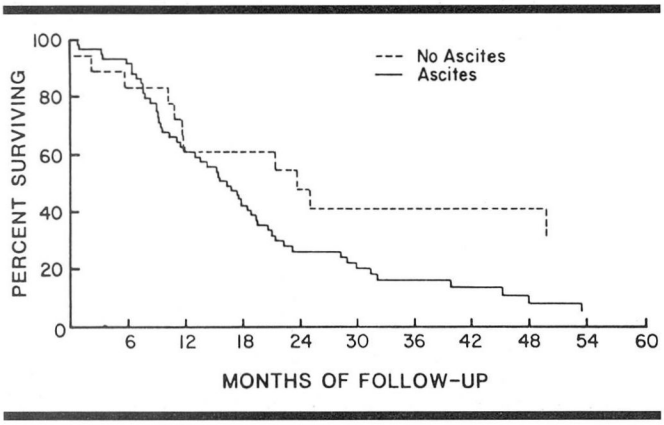

FIGURE 3. Survival of patients with ascites *v* without ascites.

months, whereas for those with Stage IV disease it was 15.9 months (*Figure 2*). The one- and three-year survival rates were 64% and 35% for Stage III patients and 54% and 21% for Stage IV patients. *Figure 3* illustrates the survival distributions for those with and without ascites. The median survival time was 16 months for women with ascites and 24 months for those without ascites. For those with ascitic fluid, the one- and three-year survival rates were 61% and 26% and for those without ascites the rates were 61% and 48%.

The effects of factors significantly related to survival within stage groups (III and IV) differed by stage. Thus, in the multivariate framework of the Cox model, stage was included in the model as a means of adjustment. When controlling for stage, debulking status (P=0.0001) and parity (P=0.04) were the two factors independently related to survival.

DISCUSSION

In the 1980s, cytoreductive surgery for epithelial ovarian cancer is an attempt to reduce tumor bulk to an "optimal" volume to gain the maximum benefits from cis-platin-containing combination chemotherapy. The probability of achieving a response from chemotherapy is largely related to the volume of tumor at the time chemotherapy is started.[4] Cytoreduction reduces a large volume of tumor that contains a high percentage of cells in the rest phase (G_o) of their cell cycle to a smaller tumor volume that contains a high percentage of actively dividing cells. The smaller tumor volume with a higher growth fraction is believed to be more vulnerable to chemotherapeutic agents.[5]

Much of this approach has evolved since 1975, when Griffiths[6] first demonstrated that survival of women with Stage II and III epithelial ovarian carcinoma was significantly related to residual disease after surgery. In 1979, the effectiveness of combination chemotherapy including cis-platin, doxorubicin hydrochloride, and cyclophosphamide was demonstrated in Stage III and IV epithelial ovarian cancer.[7] Since that time, several retrospective studies have shown increased survival by patients undergoing maximal cytoreduction followed by chemotherapy.[8–14] However, most of these studies involved small numbers of patients and/or chemotherapy regimens without cis-platin.

From 1975 through 1985 at the Cleveland Clinic, surgeons achieved optimal cytoreduction in nearly 45% of the women who presented with advanced epithelial ovarian cancer (Stage III and IV). When only women with Stage III disease are considered, the rate was improved to 55%. Ninety-one percent of these patients received a cis-platin-containing combination chemotherapy regimen after surgery. In this study, women who had Stage III disease, non- serous cell type, absence of a distended abdomen, and age less than 50 years were most likely to have optimal cytoreduction. Those who had optimal cytoreduction appeared to survive longer without significant increased risk for postoperative morbidity than those who had suboptimal cytoreduction.

It appears that after controlling for stage of disease and debulking status, women who had delivered children may be at higher risk for death than those who had been nulliparous. This unexpected finding may be an artifact resulting from the retrospective design of this study. A second explanation may be that parity was strongly associated with another risk factor for death. However, the relationship of parity with other risk factors was examined and no significant association was found. Finally, this may represent a real finding. Perhaps at a later date other studies will clarify this issue.

In various studies, the percentage of patients with advanced epithelial ovarian cancer who are able to have optimal cytoreduction ranges from 28% to 70% at initial surgery.[8–14] Location of metastatic disease and the medical status of the patient contribute to the surgeon's capacity to achieve optimal cytoreduction. When indicated, bowel surgery may be part of the cytoreductive effort. The need for bowel surgery in this study was comparable to that reported by others.[10,12,14] As corroborated in this study, bowel surgery has not increased surgical morbidity. Blythe and Wahl[15] believe that, in addition to improved survival without significant increased risk of postoperative morbidity, patients who have optimal cytoreduction benefit from a measurably improved quality of life.

During the first half of the study period, only 28% of patients had optimal cytoreduction. This figure increased to 49% during the last five years studied. While this increase may be the result of progressive surgical experience and expertise, it may also reflect an increased effort to achieve optimal cytoreduction following the introduction of platinum chemotherapy. Unfortunately, this study, as is the case with most others, cannot separate the survival benefits achieved as a result of aggressive surgery from those achieved as a result of more active chemotherapy. We suspect that it is a combination of these two factors that has resulted in the modestly improved outcome for patients with advanced ovarian cancer. Since in our experience aggressive cytoreductive surgery resulted in acceptable morbidity and mortality, we would continue to advocate the surgery in conjunction with platinum-based multi-agent chemotherapy for whatever potential benefits it offers patients.

While this study, as well as several other retrospective evaluations, supports the benefits of aggressive cytoreduction for advanced epithelial ovarian cancer, some remain skeptical of this approach. Critics[16,17] state that patients who are able to have optimal cytoreduction may have lower volumes of less aggressive tumor, resulting in a better prognosis regardless of surgery. At present, there is no accurate way to measure initial tumor volume. Prospective studies evaluating the merit of cytoreductive surgery for advanced epithelial ovarian carcinoma are underway. Until they are completed, cytoreductive surgery remains the state of the art for the treatment of this ruthless disease.

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